REMARKS

This is a response to the Office Action, dated August 4, 2009 ("Office Action"). Allowance and reconsideration of the application in view of Applicants' foregoing amendments and ensuing remarks are respectfully requested. Claim 1 has been amended; claims 1-13 and 18-23 remain pending.

Priority

Examiner maintains that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 in that the provisional application, 60/527,300, does not provide support for a targeting molecule that promotes penetration of the blood brain barrier. Although Applicants previously argued that support for the penetration of the blood brain barrier exists because the 60/527,300 provisional application recites a targeting antibody module against transferrin receptor, Examiner asserts that this is not persuasive because the transferrin receptor is not exclusively expressed on the blood brain barrier surface but are also expressed on tumor cells.

In response, Applicants submit that they are perplexed by Examiner's analysis. Applicants fail to understand how the mere fact that, in addition to targeting the blood brain barrier, the invention may also target other surfaces, is relevant to this rejection. Under 35 U.S.C. §119(e), for the non-provisional application to be afforded the priority date of the provisional application, the two applications must share at least one common inventor, and the specification of the provisional application must "contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise and exact turns," 35 U.S.C. §112, ¶1, to enable an ordinary skilled artisan to practice the invention claimed in the non-provisional application. *See New Railroad Mfg LLC v. Vermeer Mfg Co., 298 F.3d 1290, 63 USPQ2d 1843, 1846 (Fed. Cir 2002) (quoting 35 USC §119(e)(1) (Supp. 2000)), cert denied 537 U.S. 1232 (2003).*

In this instance, the provisional application describes a targeting antibody molecule for transferrin receptor. It would have been readily apparent to one of ordinary skill in the art, that a drug delivery molecule targeted to transferrin receptors would target **all** surfaces that express

transferrin receptors, including the blood brain barrier and otherwise. Transferrin receptors are known by those of skill in the art to be expressed on endothelium cell surfaces of the blood brain barrier. As noted in the present application, in vitro and in vivo studies indicate that transferrin receptor may be used as an anchorage for a drug delivery system chemically bound to transferrin or mAV OX-26 or any other appropriate mAB that binds the transferrin receptor and thereby achieves transcytosis through blood brain barrier (BBB). *See page 4, lines 26-29, citing Nielson, Methods Enzymol, 340: 329-340; Friden, J.Controlled Release 46:117-128; Van Gelder, Brain Research 746:105-116; Li, Medical Research Reviews 22:225:250; Lee, J.Pharmacol.Exp.Therapeut. 292:1048-1052; Friden, Proc.Natl.Acad.Sci. 88:4771-4775; Zhang, Clinical Cancer Research 10:3667:3677.* The provisional application describes a drug delivery molecule directed toward targeting molecules that promote penetration of the blood brain barrier, enabling an ordinary skilled artisan to practice the invention as claimed in the present application. Thus, Applicants submit that the present application is entitled to the priority date of December 5th, 2003.

35 U.S.C. §103(a) – Claims 1-13 and 20

Examiner maintains previous rejections of claims 1-13 and 20 under 35 U.S.C. §103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*

Examiner asserts that although the scaffold described by LaFleur, *et al.* is not covalently linked to active modules, Cammas, *et al.* is relied upon to teach covalent linkage. Examiner also asserts that Cammas, *et al.* teaches that the introduction of biologically active molecules or targeting moieties can be accomplished by appropriate modifications. In response, Applicants submit that Cammas, *et al.* does **not** teach covalent attachment to the claimed active modules and that Examiner fails to understand some of the differences between the cited prior art and the present invention as claimed regarding their respective chemical structures and fundamental principles of chemistry.

The Federal Circuit has noted that "references that teach away cannot serve to create a prima facie case of obviousness...If references taken in combination would produce a 'seemingly inoperative device,' we have held that such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 60 USPQ2d 1001, 1010 (Fed. Cir. 2001); In*

re Sponnoble, 405 F.2d 578, 587, 160 USPQ 237, 244 (CCPA 1969); In re gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

In this instance, Applicants submit that the combination of Cammas, *et al.* and LaFleur, *et al.* would produce a seemingly inoperative device. Cammas, *et al.* describes synthesis of various forms of polymalic acid conjugated to conjugates by anionic ring-opening polymerization of maloactonic acid esters appropriately derivatized at the alpha-carboxylic group in the monomer before polymerization. Attachment of proteins and nucleic acids via ring open polymerization of corresponding malolactonic derivatives, such as that described by Cammas, *et al.*, is not chemically possible. The product would be inactive in targeted drug delivery due to the degradability and reactivity of proteins and nucleic acids in uncontrolled side reactions during the polymerization reaction. In contrast, the present application describes how to covalently attach a plurality of durable (e.g. PEG, amino acids, spacers) and non durable (e.g. proteins and nucleic acids) molecules in a hierarchic mode to polymalic acid, starting with highly purified naturally occurring beta-poly (L-malic acid) produced by Physarum polycephalum. *See page 6, lines 27-34 and page 7, lines 1-6.* The present application, unlike Cammas, *et al.*, activates all pendant carboxylates in nonaqueous solvent, then introduces a first round of chemically durable groups via amide bond formation at these activated carboxylates and by introducing reactive sulfhydryl groups. Then, in a second round of synthesis, the less durable groups (e.g. nucleic acids and proteins) are introduced by reaction with sulfhydryles forming either disulfide bonds or thioether bonds. *See page 7, lines 9-26.* Because a novel and completely different kind of chemistry is used in the present application, the invention as claimed allows covalent attachment of polynucleotides and polypeptides whereas Cammas, *et al.* does not. However, in the interest of expediting prosecution, Applicants have amended the relevant claims so that the invention is now limited to a drug delivery molecule wherein at least one active module comprises a polypeptide and/or polynucleotide, although Applicants in no way concede such an amendment is necessary to overcome the cited prior art.

In light of the present amendment and aforementioned remarks, Applicants submit that claims 1-13 and 20 under 35 U.S.C. §103(a) are patentable over the combination of LaFleur, *et al.* and Cammas, *et al.* and would not have been obvious to one of skill in the art.

35 U.S.C. §103(a) – Claims 18-19

Examiner maintains previous rejections of claims 18 and 19 under 35 U.S.C. § 103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*, and further in view of Saito, *et al.* Examiner asserts that one of skill in the art would find it obvious that the disulfide bonds taught by Saito, *et al.* would be appropriate for linking antisense oligonucleotides to the polymalic acid polymer. In response, in light of the present amendment and reasons discussed above, Applicants respectfully submit that the present invention would have been nonobvious at the time of filing to one of skill in the art in light of the combination of LaFleur, *et al.*, Cammas, *et al.* and further in view of Saito, *et al.*

35 U.S.C. §103(a) – Claim 21

Examiner maintains previous rejections of claim 21 under 35 U.S.C. § 103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*, and further in view of Summerton, *et al.* Examiner asserts that it would have been obvious to one of skill in the art to incorporate morpholino antisense oligonucleotides for the modified antisense oligonucleotides taught by LaFleur, *et al.*, because Summerton, *et al.* teaches the benefits of using such morpholino antisense oligonucleotides. In response, Applicants respectfully submit that the present invention would not have been obvious to one of skill in the art in light of the combination of LaFleur, *et al.* and Cammas, *et al.*, and further in view of Summerton, *et al.* in light of the present amendment and reasons discussed above.

35 U.S.C. §103(a) – Claims 22-23

Examiner maintains previous rejections of claims 22 and 23 under 35 U.S.C. § 103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*, and further in view of Khazenzon, *et al.* Examiner asserts that Khazenzon, *et al.* teaches morpholino antisense oligonucleotides targeting α4-laminin, and it would have been obvious to one of skill in the art to formulate the antisense oligonucleotides described by Khazenzon, *et al.* in the polymalic acid drug delivery molecule taught by LaFleur, *et al.* and Cammas, *et al.* In response, Applicants respectfully submit that the present invention would not have been obvious to one of skill in the art in light of the combination of LaFleur, *et al.* and Cammas, *et al.*, and further in view of Khazenzon, *et al.* in light of the present amendment and reasons discussed above.

All of the claims in the application are believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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